ICSI for non-male indications

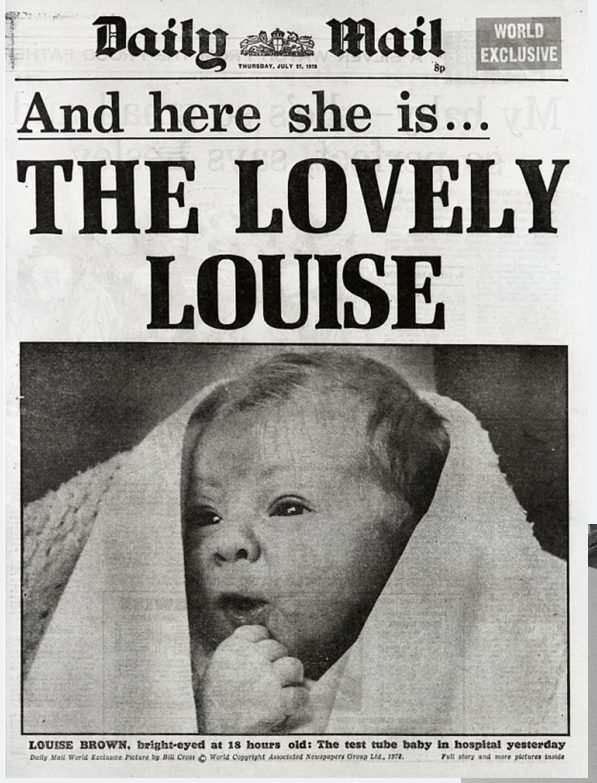
Neelke De Munck

26/10/2022

Brussels IVF
BSRM Belgian Society for Reproductive Medicine
VUB Vrije Universiteit Brussel
Universitair Ziekenhuis Brussel

No conflicts to declare

Some history …



Daily Mail

THURSDAY, JULY 27, 1978

8p

WORLD EXCLUSIVE

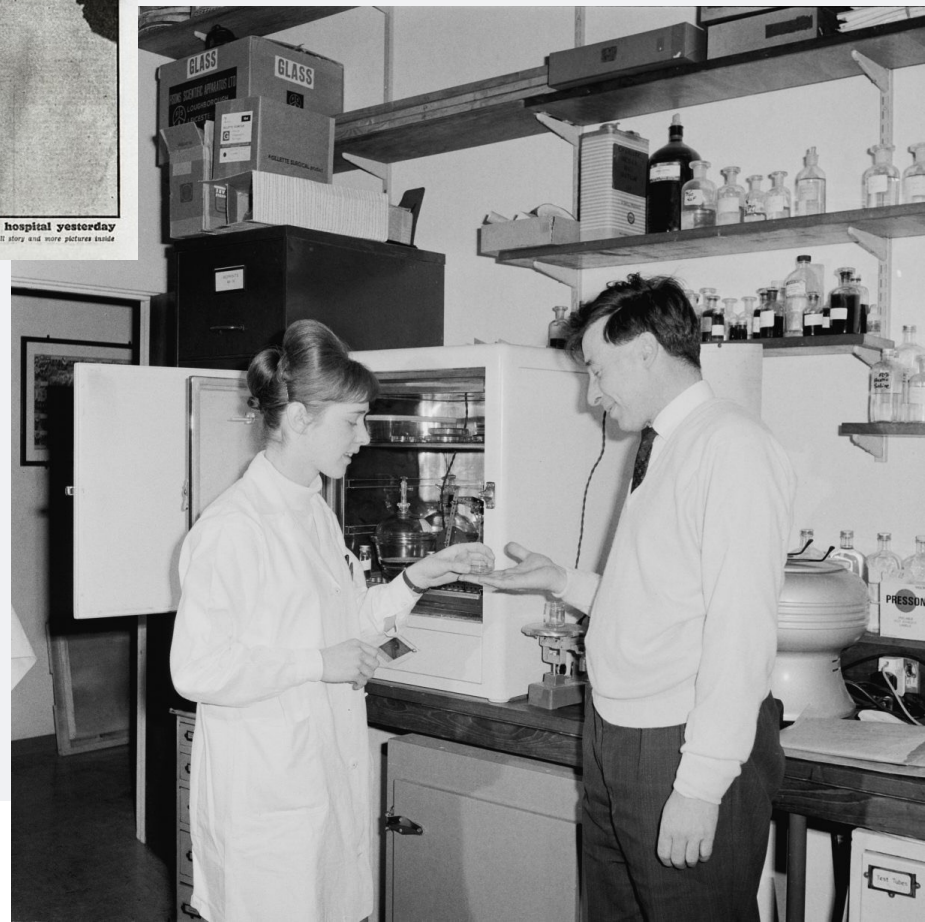
And here she is…

THE LOVELY LOUISE

LOUISE BROWN, bright-eyed at 18 hours old: The test tube baby in hospital yesterday

Daily Mail World Exclusive Picture by Bill Cross © World Copyright Associated Newspapers Group Ltd., 1978.

Full story and more pictures inside



Some history …

The Lancet · Saturday 3 December 1983

CURRENT STATUS OF IN-VITRO FERTILISATION AND IMPLANTATION OF HUMAN EMBRYOS

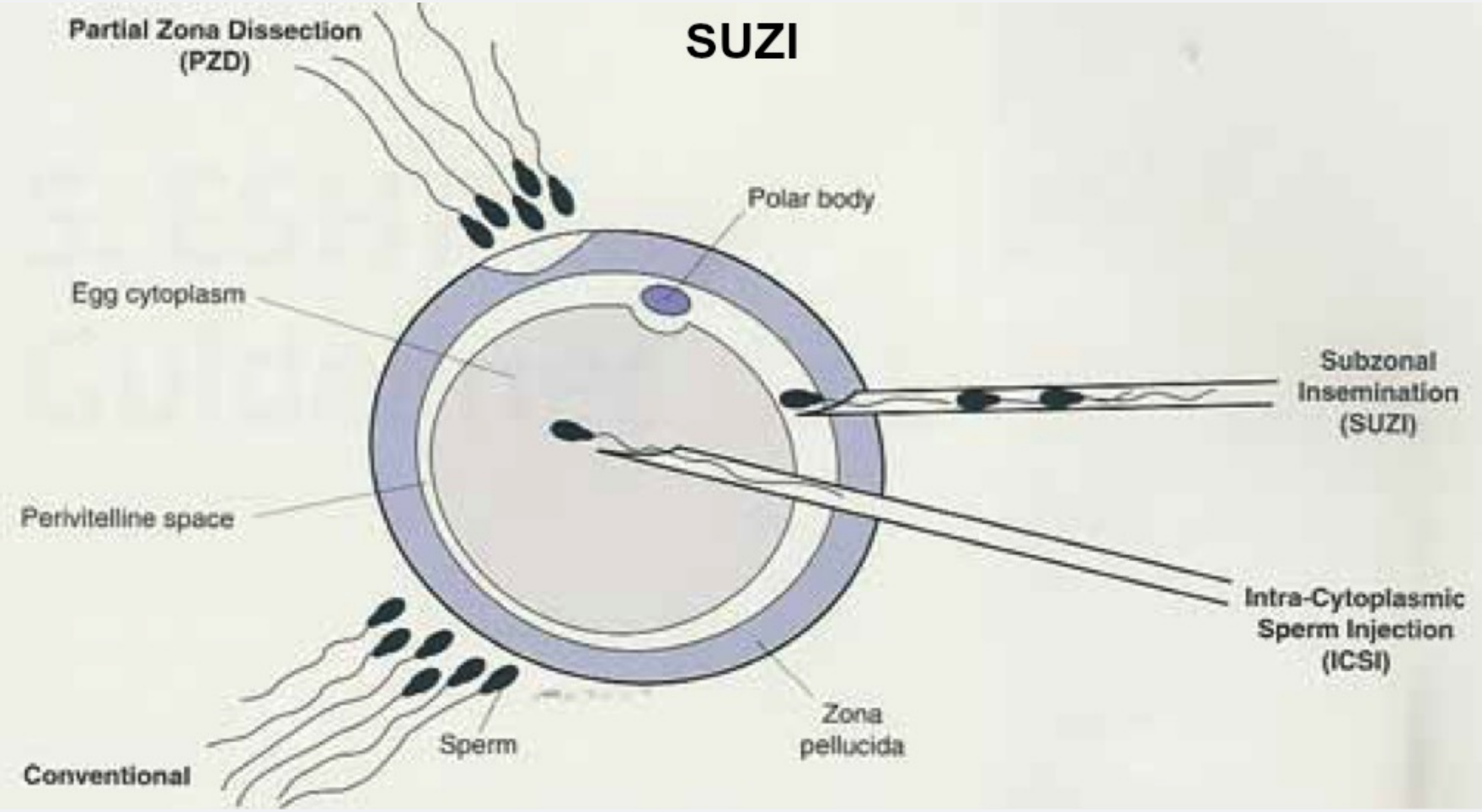
R. G. EDWARDS P. C. STEPTOE

Physiological Laboratory, Cambridge University, and Bourn Hall, Cambridge

Summary Between October, 1980, and April, 1983, embryos fertilised in vitro were replaced in the uteri of 1200 women. The "clinical" pregnancy rate rose from 16·5% from October, 1980, until September, 1982, to almost 30% in 1983. The proportion of pregnancies ending in abortion varied from 25–35%. Factors favourably modifying implantation rate were maternal age of under 40 years, priming with clomiphene alone, and the replacing of more than one embryo in the uterus. The replacing of two or more embryos, increasing maternal age, a poor obstetric history, and high levels of follicular oestrogens raised the chances of abortion.

aspects human IVF. By 1986, it was estimated that 2,000 babies had been born world wide, 1,000 of these from Bourn Hall, and the team there published their observations on their first 500 births in Human Reproduction in 1986 (Steptoe et al., 1986).

The way to ICSI



Fertilization of Human Oocytes by Sperm From Infertile Males After Zona Pellucida Drilling

J. W. Gordon, B. E. Talansky, L. Grunfeld, C. Richards, G. J. Garrisi and N. Laufer, *Department of Obstetrics, Gynecology and Reproductive Science, Mt. Sinai School of Medicine, New York, New York*

Fertil. Steril., **50:** 68–73, 1988

Fertilization in Trypsin-Treated Oocytes

Ann A. Kiessling, Dimitris Loutradis,[a] Patricia M. McShane, and Katharine V. Jackson

IMPLANTATION OF EMBRYOS AFTER PARTIAL OPENING OF OOCYTE ZONA PELLUCIDA TO FACILITATE SPERM PENETRATION

Jacques Cohen
Henry Malter
Carole Fehilly
Graham Wright
Carlene Elsner
Hilton Kort
Joe Massey

Reproductive Biology Associates, and Department of Gynecology and Obstetrics, Emory University, Atlanta, Georgia 30342, USA

Blastocyst Formation and Hatching In Vitro Following Zona Drilling of Mouse and Human Embryos

Gamete Research 24:67–80 (1989)

Henry E. Malter and Jacques Cohen

Twin birth after subzonal insemination

S. Fishel
S. Antinori
P. Jackson
J. Johnson
F. Lisi
F. Chiariello
C. Versaci

ICSI

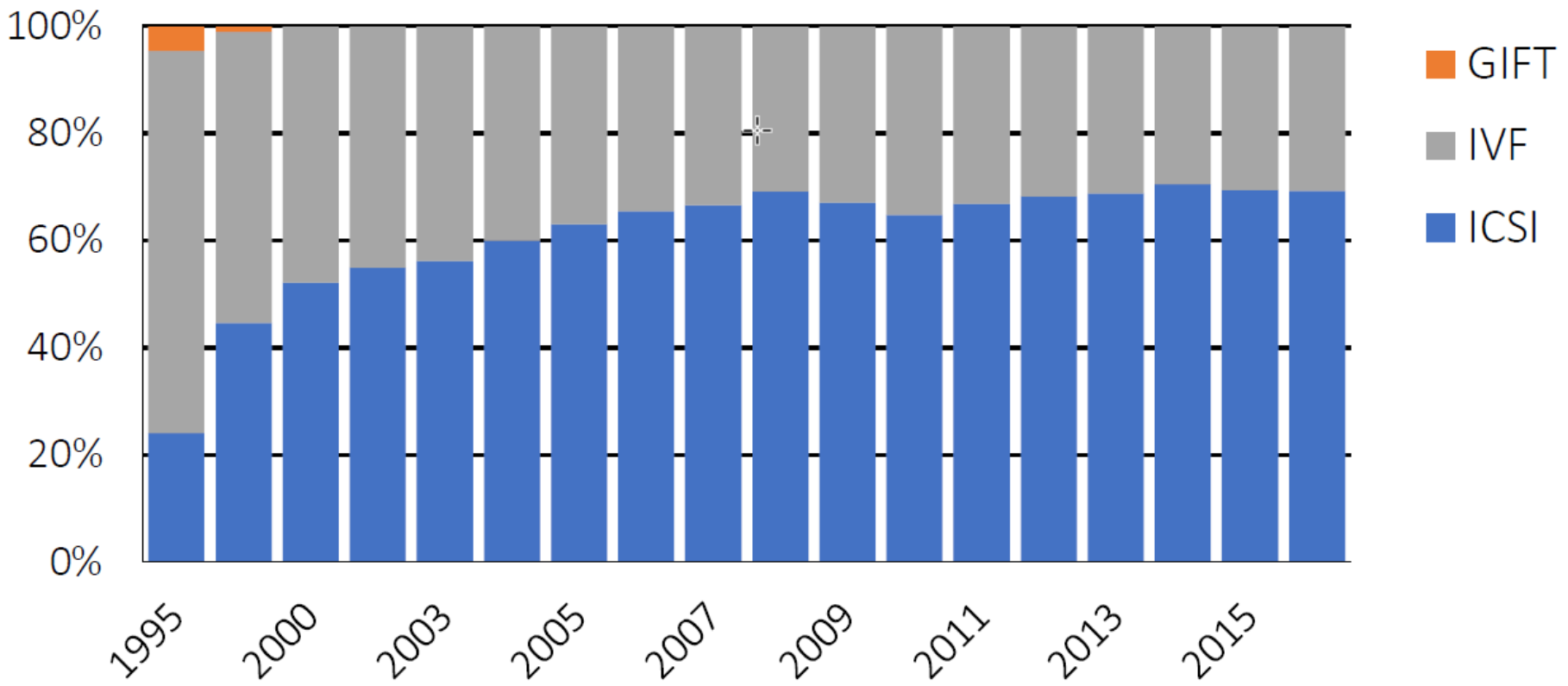
Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte

GIANPIERO PALERMO HUBERT JORIS
PAUL DEVROEY ANDRE C. VAN STEIRTEGHEM

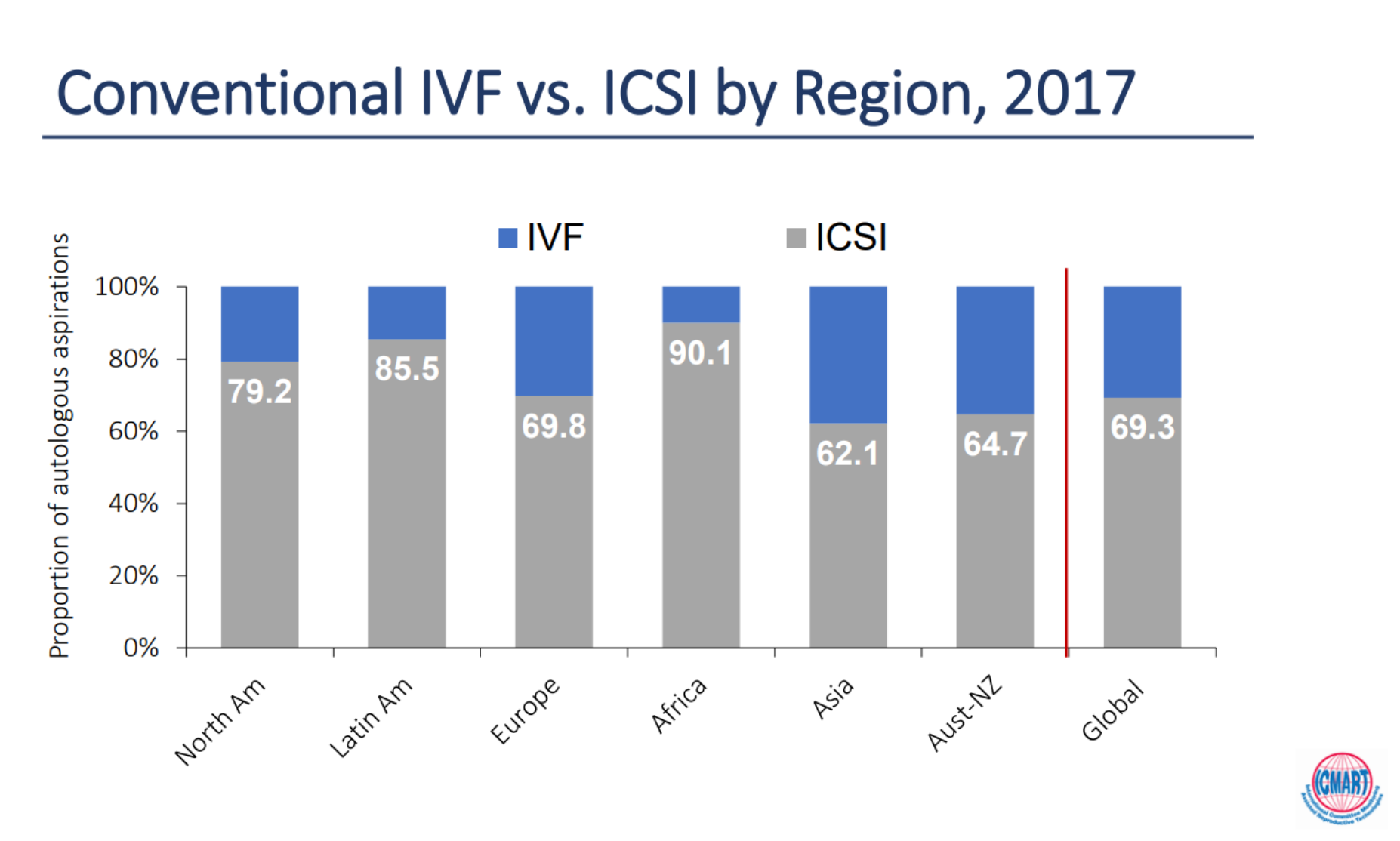
VOL 340: JULY 4, 1992 THE LANCET

Since 1992

Trends: Conventional IVF vs. ICSI

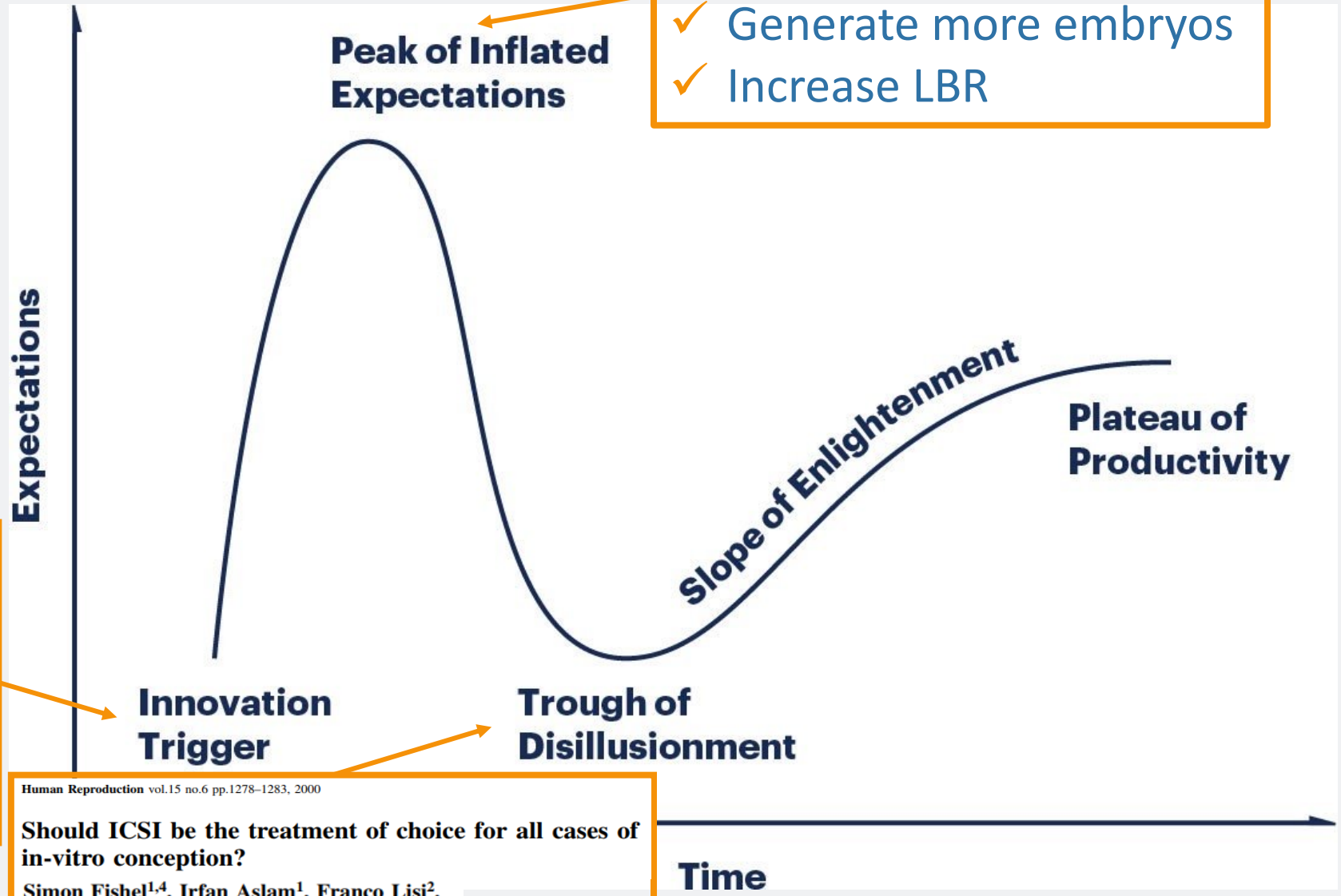


ICSI-IVF: 2017



Gartner hype cycle - ICSI

- ✓ Avoid TFF
- ✓ Increase fertilisation
- ✓ Generate more embryos
- ✓ Increase LBR



Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte

GIANPIERO PALERMO HUBERT JORIS
PAUL DEVROEY ANDRE C. VAN STEIRTEGHEM

VOL 340: JULY 4, 1992 THE LANCET

Human Reproduction vol.15 no.6 pp.1278–1283, 2000

Should ICSI be the treatment of choice for all cases of in-vitro conception?

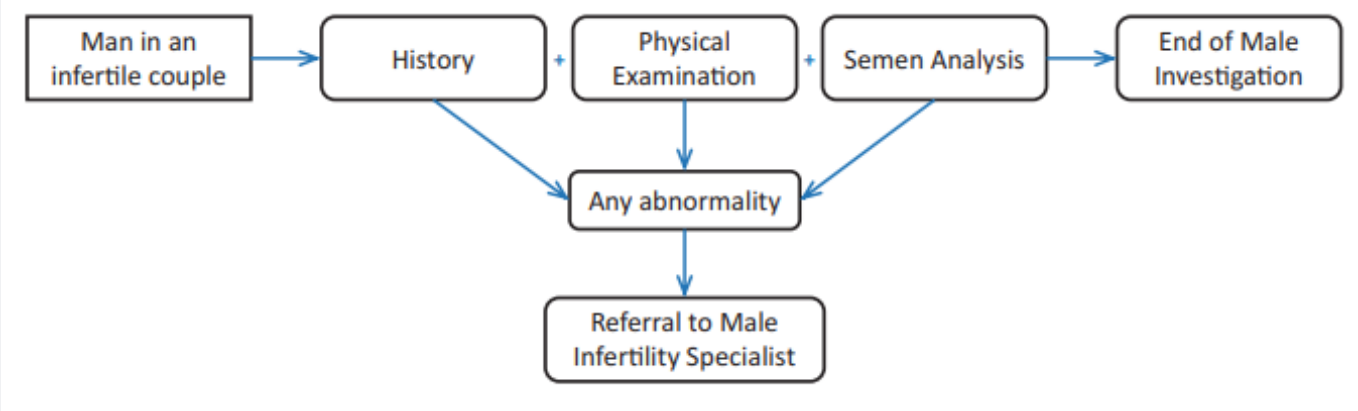
Simon Fishel[1,4], Irfan Aslam[1], Franco Lisi[2], Leonardo Rinaldi[2], Judy Timson[1], Merwyn Jacobson[3], Lawrence Gobetz[3], Steve Green[1], Alison Campbell[1] and Rosella Lisi[2]

Human Reproduction Update, Vol.23, No.6 pp. 660–680, 2017
Advanced Access publication on July 19, 2017 doi:10.1093/humupd/dmx021

human reproduction update

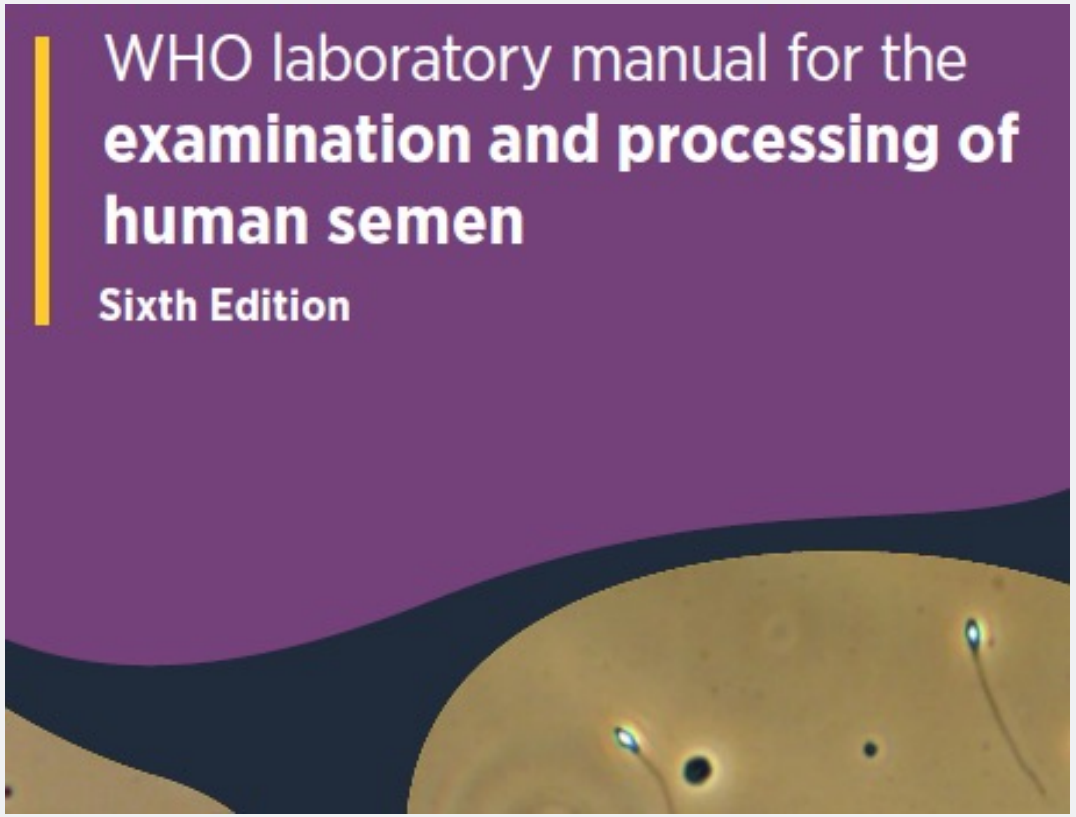
The diagnosis of male infertility: an analysis of the evidence to support the development of global WHO guidance—challenges and future research opportunities

Christopher L.R. Barratt[1], Lars Björndahl[2], Christopher J. De Jonge[3], Dolores J. Lamb[4], Francisco Osorio Martini[5], Robert McLachlan[6], Robert D. Oates[7], Sheryl van der Poel[8,9], Bianca St John[10], Mark Sigman[11], Rebecca Sokol[12], and Herman Tournaye[13]



EAU Guidelines on Sexual and Reproductive Health

A. Salonia (Chair), C. Bettocchi, J. Carvalho, G. Corona, T.H. Jones, A. Kadioğlu, J.I. Martinez-Salamanca, S. Minhas (Vice-chair), E.C. Serefoğlu, P. Verze
Guidelines Associates: L. Boeri, P. Capogrosso, A. Cocci, K. Dimitropoulos, M. Gül, G. Hatzichristodoulou, A. Kalkanli, L.A. Morgado, V. Modgil, U. Milenkovic, G. Russo, T. Tharakan
Guidelines Office: J.A. Darraugh



https://uroweb.org/guidelines/sexual-and-reproductive-health/

What is non-male factor?

normozoospermia	total number (or concentration, depending on outcome reported)* of spermatozoa, and percentages of progressively motile (PR) and morphologically normal spermatozoa, equal to or above the lower reference limits

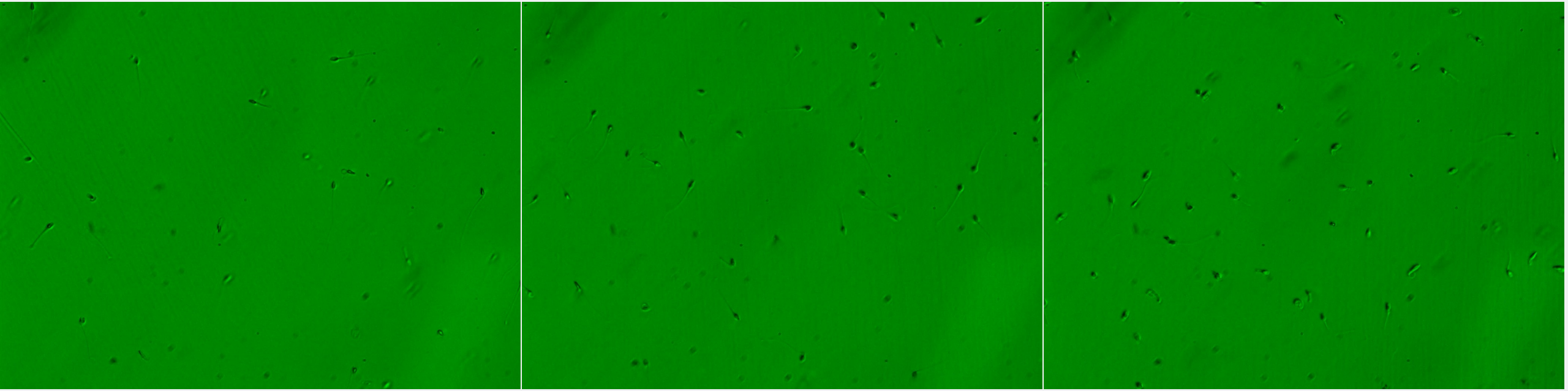
Table 1 | **Lower reference limits of basic semen analysis parameters from consecutive World Health Organization semen analysis manuals**

Manual	Semen volume (ml)	Sperm concentration ($\times 10^6$/l)	Total sperm number ($\times 10^6$)	Total motility (%)	Progressive motility (%)	Normal forms (%)	Vitality (%)
1980 (first edition)	NR	20–200	NR	60	NR	80.5	NR
1987 (second edition)	2	20	40	50	25	50	50
1992 (third edition)	2	20	40	50	25[a]	30	75
1999 (fourth edition)	2	20	40	50	25[a]	14[b]	75
2010 (fifth edition)[c]	1.5	15	39	40	32	4[b]	58
2021 (sixth edition)[c]	1.4	16	39	42	30	4[b]	54

NR, not reported. [a]Grade 'a'. [b]Strict (Kruger) morphology. [c]Fifth percentile of the distribution of semen analysis results from men in couples who started a natural pregnancy that resulted in a live birth delivery within 1 year of unprotected sexual intercourse.

WHO, 5th edition; Esteves, 2022

What is non-male factor?



Current guidelines?

eshre
SCIENCE MOVING PEOPLE MOVING SCIENCE

Published 23 July 2020

As registry data presented at ESHRE's online annual meeting continue to show, ICSI remains by far the world's favoured fertilisation method, even in non-male factor cases. Updated guidelines still cannot justify the trend.

Intracytoplasmic sperm injection (ICSI) for non–male factor indications: a committee opinion

Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology

American Society for Reproductive Medicine and Society for Assisted Reproductive Technology, Birmingham, Alabama

CONCLUSIONS

- ICSI without male factor infertility may be of benefit for select patients undergoing IVF with preimplantation genetic testing for monogenic disease and previously cryopreserved oocytes.
- The additional cost burden of ICSI for non–male factor indications, where data on improved live-birth outcomes over conventional insemination are limited or absent, must be considered.

Fertility and Sterility® Vol. 114, No. 2, August 2020

sart

SART CORS (Society for Assisted Reproductive Technology Clinical Outcome Reporting System) reports (SART, 2016). The most recent SART CORS report, over 2013, shows that in the USA, among patients without diagnosed male factor infertility, in every single age group below 43, ICSI resulted in *fewer* live births than IVF (SART, 2016). The American

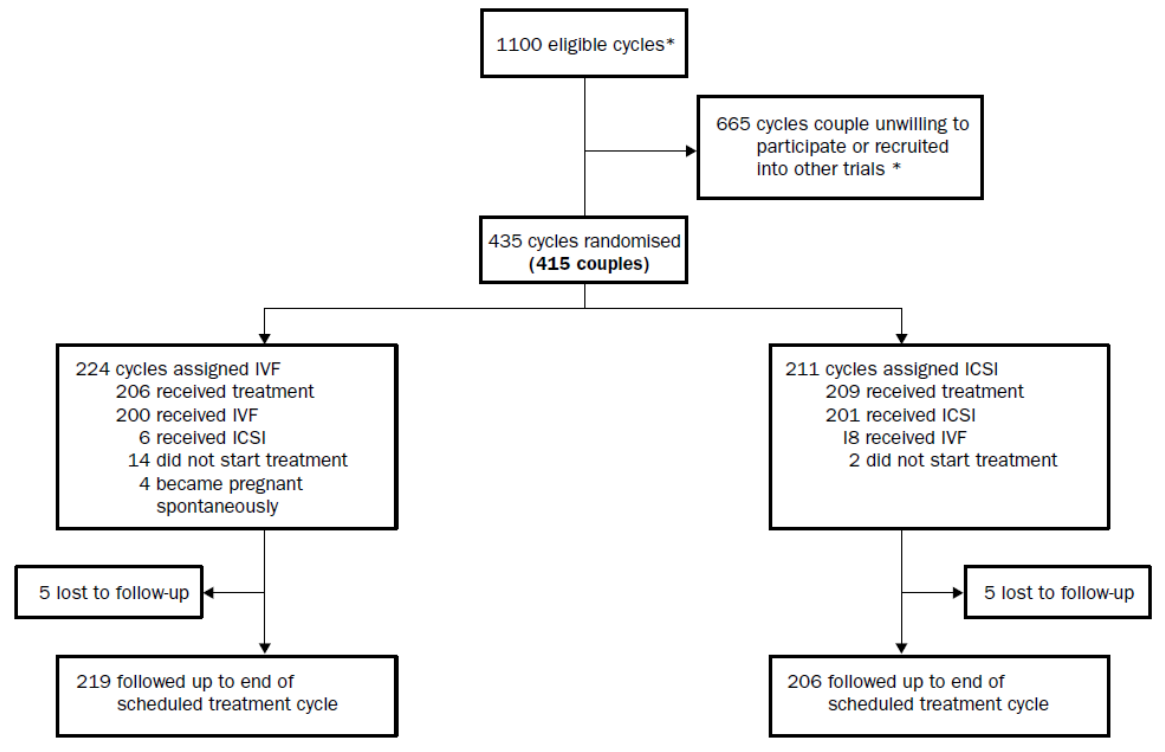
From: Evers., 2016

What do we know?

Conventional in-vitro fertilisation versus intracytoplasmic sperm injection for the treatment of non-male-factor infertility: a randomised controlled trial

Lancet 2001; **357:** 2075–79

S Bhattacharya, M P R Hamilton, M Shaaban, Y Khalaf, M Seddler, T Ghobara, P Braude, R Kennedy, A Rutherford, G Hartshorne, A Templeton



Inclusions:

- <37 years
- Non-severe male infertility:
  - Density ≥ 20 x 10^6/ml
  - Progressive motility ≥ 40%
  - Morphology: >10% (>4% allowed)

Methods:

- DET or TET
- Day 2 transfer
- DGC
- IVF: method??

	IVF (n=206)	ICSI (n=209)	95% CI for difference
Duration of stimulation in days*	12·6 (2·5)	12·2 (2·2)	−0·05 to 0·85
Oocytes collected*	11·0 (7·1)	11·0 (6·8)	−1·34 to 1·34
Oocytes inseminated or injected*	11·0 (7·1)	9·6 (5·2)	−2·91 to −0·48
Fertilised (2PN) oocytes*	6·9 (4·5)	6·3 (3·6)	−0·26 to 1·35
Cleaved embryos*	5·5 (3·3)	5·4 (2·9)	−0·60 to 0·80
Fertilisation rate (per oocyte retrieved)	1199/2065 (58%)	1003/2153 (47%)	8·5 to 14·5
Fertilisation rate (per oocyte inseminated/injected)*	1199/2065 (58%)	1003/1533 (65%)	−10·0 to −4·0
Failed fertilisation†	11 (5%)	4 (2%)	−0·3 to 7·5
Two embryo transfers†	143/159 (90%)	138/159 (87%)	−3 to 10
Transfer of two grade 1 embryos†	77/159 (48%)	68/164 (40%)	−4 to 19
Laboratory time (min)*	22·9 (12·1)	74·0 (38·1)	−56·6 to −45·6

	IVF (n=219)	ICSI (n=204)	Relative risk (95% CI)
Implantation rate*	95/318 (30%)	72/325 (22%)	1·35 (1·04–1·76)
Clinical pregnancy	72 (33%)	53 (26%)	1·27 (0·95–1·72)
Multiple pregnancy	17 (24%)	16 (30%)	0·78 (0·43–1·40)

*Analysis based on embryo as unit of analysis. 95% CI not adjusted for clustering of embryos within women.

Table 3: **Outcome of treatment**

Interpretation ICSI offers no advantage over IVF in terms of clinical outcome in cases of non-male-factor infertility. Our results support the current practice of reserving ICSI only for severe male-factor problems.

Cochrane Library

Cochrane Database of Systematic Reviews

Intra-cytoplasmic sperm injection versus conventional techniques for oocyte insemination during in vitro fertilisation in couples with non-male subfertility (Review)

van Rumste MME, Evers JLH, Farquhar C

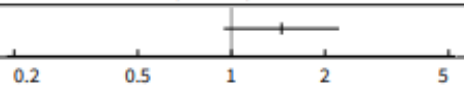
2003

Comparison 1. ICSI versus IVF

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancy rate	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 ICSI versus IVF, Outcome 1 Pregnancy rate.

Study or subgroup	IVF n/N	ICSI n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Bhattacharya 2001	70/213	51/202		1.45[0.95,2.22]

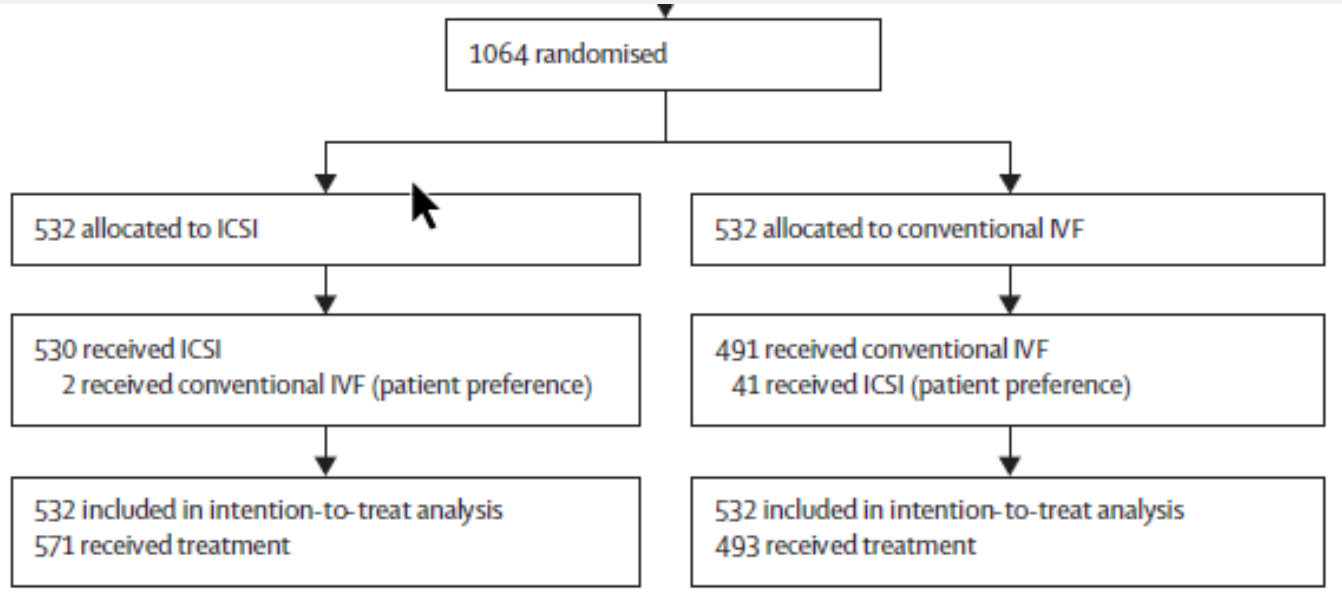


What do we know?

Intracytoplasmic sperm injection versus conventional in-vitro fertilisation in couples with infertility in whom the male partner has normal total sperm count and motility: an open-label, randomised controlled trial

Lancet 2021; 397: 1554–63

Vinh Q Dang, Lan N Vuong, Tam M Luu, Toan D Pham, Tuong M Ho, Anh N Ha, Binh T Truong, Anh K Phan, Dung P Nguyen, Thanh N Pham, Quan T Pham, Rui Wang, Robert J Norman, Ben W Mol



Outcome measures

Primary outcome

Our primary outcome will be ongoing pregnancy leading to live birth after the first embryo transfer. Live birth will be defined as a delivery of one or more living infants.[17]

Inclusions:

- 1st-2nd cycle
- Non-severe male infertility:
  - Total Sperm Count ≥ 39 x 10^6
  - Progressive motility ≥ 32%
  - Morphology: not considered

Methods:

- ICSI: DGC: 3-4h after OPU
- IVF: DGC + Swim-up: 2h after OPU for 2h: 100.000 motile sperm/ml
- SET or DET: patient's choice
- Day 3 and Day 5: physician's choice

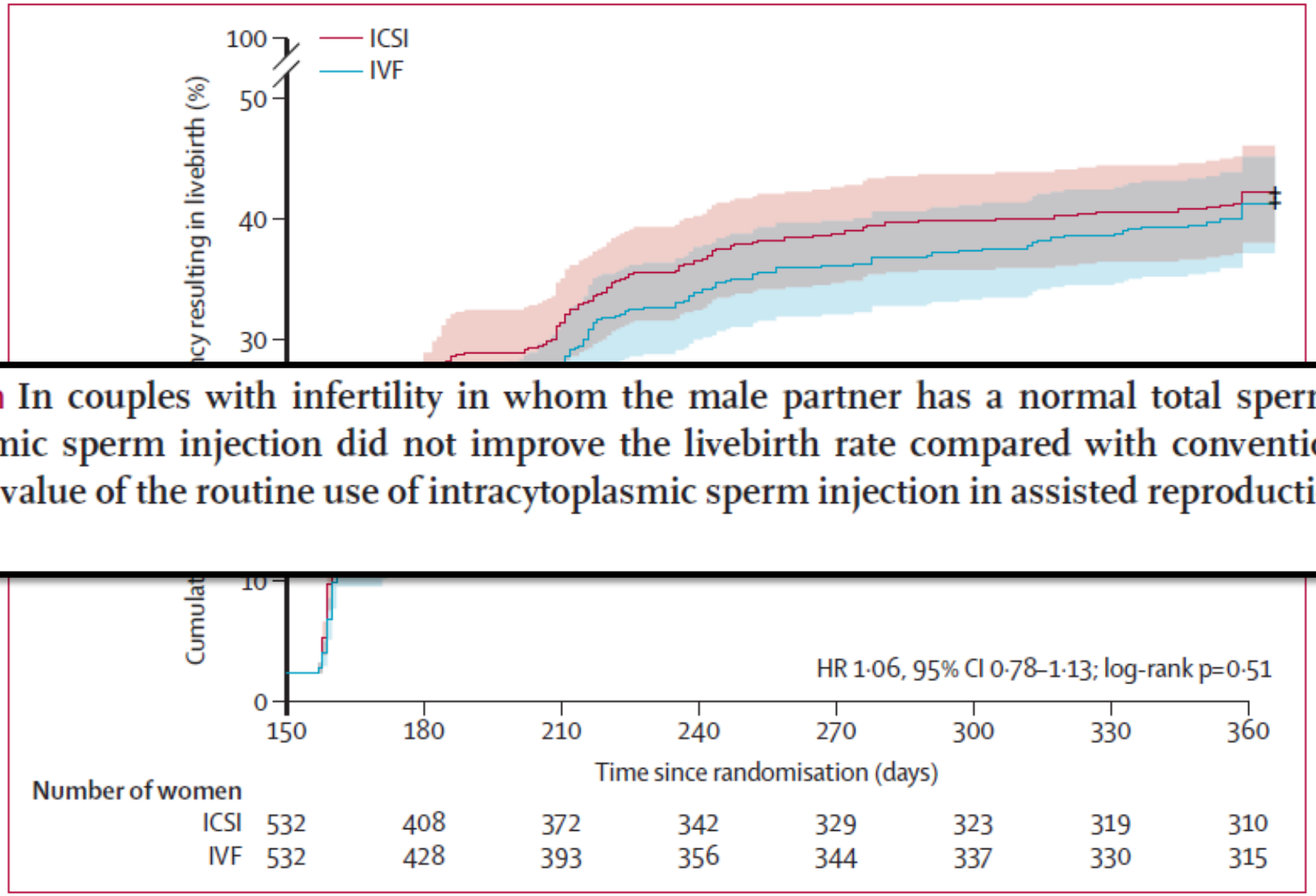


Figure 2: Kaplan-Meier graph of cumulative ongoing pregnancy resulting in livebirth (intention-to-treat population)
ICSI=intracytoplasmic sperm injection. HR=hazard ratio. IVF=in-vitro fertilisation.

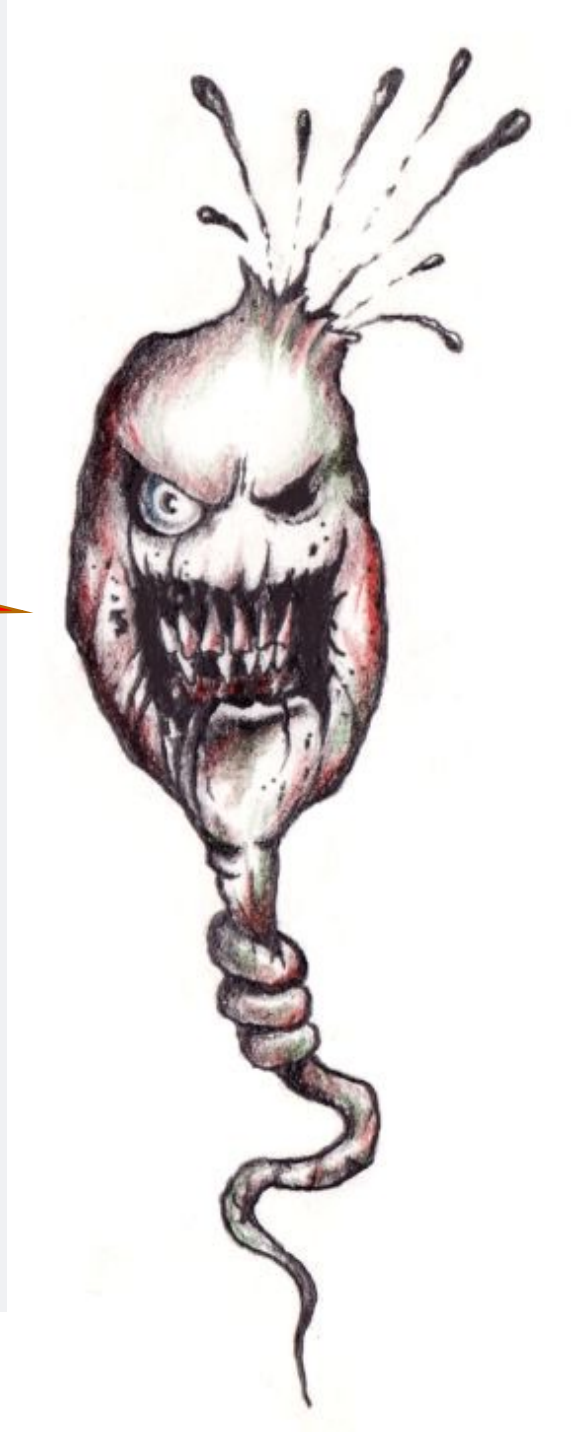
Interpretation In couples with infertility in whom the male partner has a normal total sperm count and motility, intracytoplasmic sperm injection did not improve the livebirth rate compared with conventional IVF. Our results challenge the value of the routine use of intracytoplasmic sperm injection in assisted reproduction techniques for this population.

Non-male factor infertility

	Fertilization rate IVF-ICSI	Clinical Pregnancy Rate IVF-ICSI	Live birth rate IVF-ICSI
Li et al., 2018	59.8%-56.2% (<0.001)		37.0%-36.0% aOR (95%CI): 0.99 (0.92-1.06)
Supramaniam et al., 2020		aOR (956%CI): 1.04 (0.97-1.12)	aOR (95%CI): 1.03 (0.96-1.11)
Drakopoulus et al., 2018	66.6%-66.6% (0.08)		17.8%-12.5% (0.16)
Foong et al 2006	77.2%-82.4% (NS)	50.0%-50.0% (NS)	46.7%-50.0% (NS)
Kim et al., 2014	83.4%-79.1% (0.04)/MII	23.8%-39.4% (0.001)	
Eftekhar et al., 2012	66.22%-57.46% (0.036)	35.7%-21.5% (0.031)	
Frimstad et al., 2016	49.1%-57.5% (95% CI: 0.97-1.35)	48.4%-41.6% (95% CI: 0.70-0.86)	39.6%-33.0% (95% CI: 0.69-0.85)
Schwarze et al., 2017	73.55%-73.84% (<0.001)		28.76%-22.9% (<0,0001)
Sustar et al., 2019	67.1%-62.3% (<0.0001)	26.83%-19.85% (<0.001)	17.22%-13.2% (0.001)

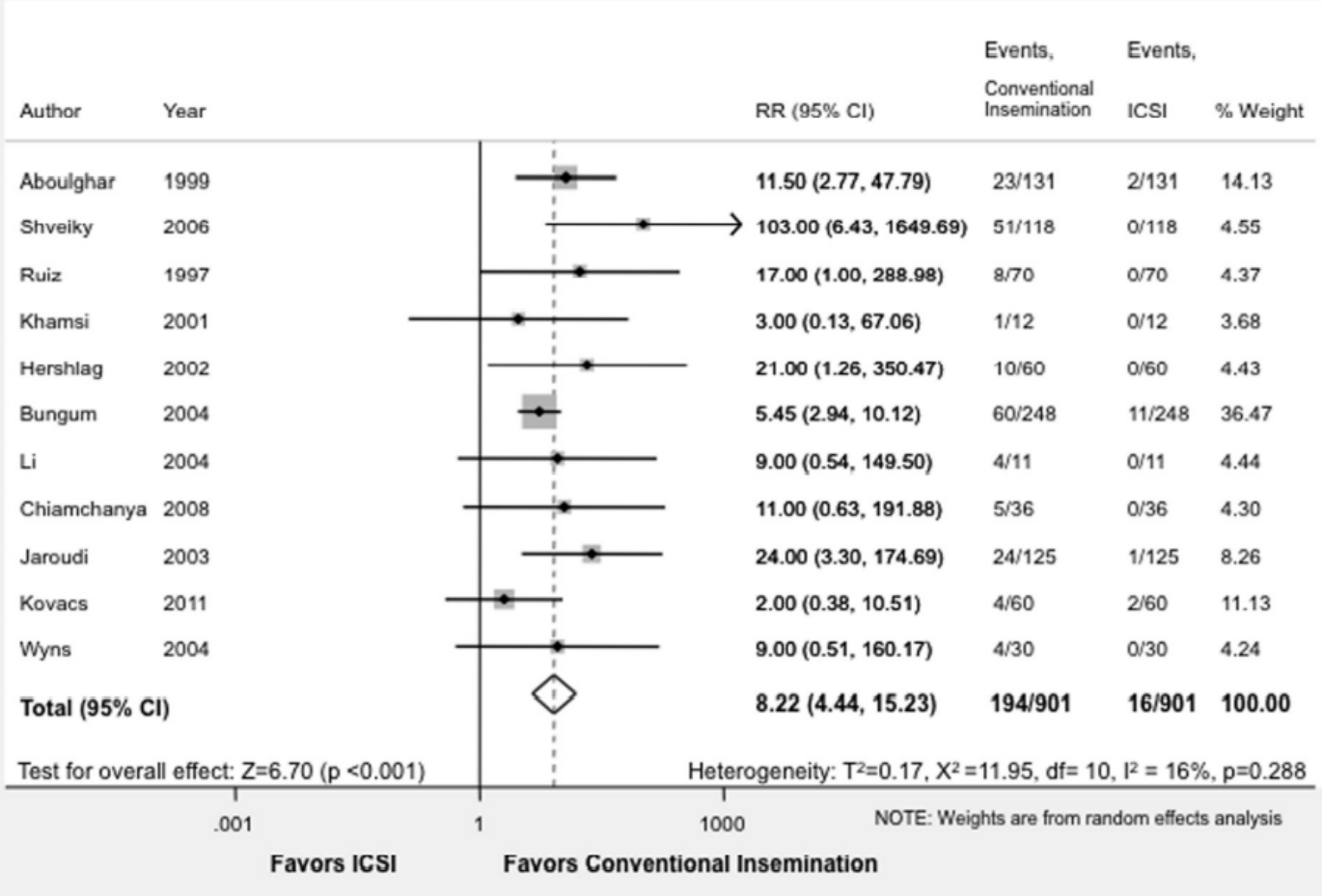
Why are we scared of IVF?

Total
Fertilization
Failure



Total Fertilization Failure

TFF in sibling oocytes



Does intracytoplasmic sperm injection improve the fertilization rate and decrease the total fertilization failure rate in couples with well-defined unexplained infertility? A systematic review and meta-analysis

2013

Lauren N. C. Johnson, M.D.,[a] Isaac E. Sasson, M.D., Ph.D.,[c] Mary D. Sammel, Sc.D.,[b] and Anuja Dokras, M.D., Ph.D.[a]

Total Fertilization failure

Higher clinical pregnancy rate with in-vitro fertilization versus intracytoplasmic sperm injection in treatment of non-male factor infertility: Systematic review and meta-analysis

Ahmed M. Abbas[a,*], Reda S. Hussein[a,b], Mohamed A. Elsenity[c], Ihab I. Samaha[d], Karim A. El Etriby[d], Mohamed F. Abd El-Ghany[e], Mansour A. Khalifa[a], Shaimaa S. Abdelrheem[f], Amal Abdrabbo Ahmed[g], Mostafa M. Khodry[e]

Journal of Gynecology Obstetrics and Human Reproduction 49 (2020) 101706

Study or Subgroup	IVF Events	IVF Total	ICSI Events	ICSI Total	Weight	Risk Ratio M-H, Random, 95% CI
Aboulghar et al, 1996	5	22	0	22	4.2%	11.00 [0.64, 187.67]
Bhattacharya et al 2001	11	206	4	209	9.7%	2.79 [0.90, 8.62]
Bungum et al,2004	60	185	11	60	11.9%	1.77 [1.00, 3.14]
Foong et al, 2006	2	30	4	30	7.7%	0.50 [0.10, 2.53]
Hershlag et al, 2002	10	60	0	60	4.3%	21.00 [1.26, 350.47]
Hwang et al, 2005	9	60	0	60	4.2%	19.00 [1.13, 319.27]
Jaroudi et al, 2003	24	125	1	125	6.4%	24.00 [3.30, 174.69]
Kim et al, 2007	19	597	4	99	10.0%	0.79 [0.27, 2.27]
Kim et al, 2007 (b)	1	154	6	142	6.0%	0.15 [0.02, 1.26]
Komsky-Elbaz et al, 2013	49	387	7	399	11.1%	7.22 [3.31, 15.74]
Ruiz et al, 1997	8	70	0	70	4.2%	17.00 [1.00, 288.98]
Staessen et al, 1999	7	56	2	56	8.1%	3.50 [0.76, 16.12]
Tannus et al, 2016	23	255	48	490	12.2%	0.92 [0.57, 1.48]
Total (95% CI)		**2207**		**1822**	**100.0%**	**2.63 [1.29, 5.35]**
Total events	228		87			

Heterogeneity: Tau² = 1.02; Chi² = 51.08, df = 12 (P < 0.00001); I² = 77%

Test for overall effect: Z = 2.67 (P = 0.008)

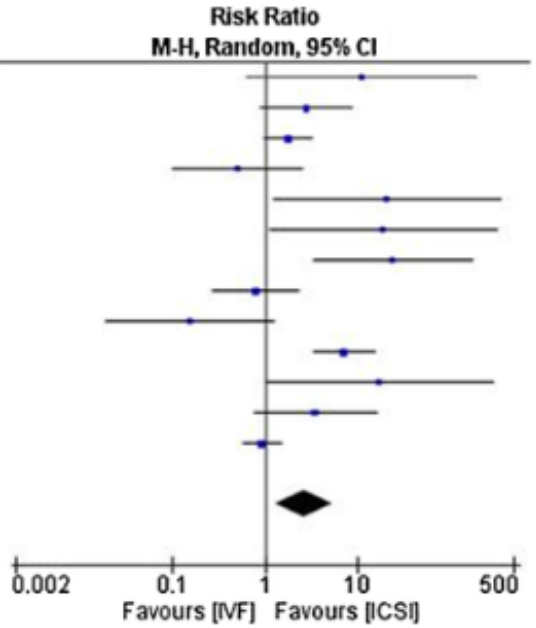


Fig. 6. Forest plot for the total fertilization failure rate.

Fertilization failure

Reinsemination by intracytoplasmic sperm injection of 1-day-old oocytes after complete conventional fertilization failure

Paula C. Morton, B.S.
Cynthia S. Yoder, B.S.
Michael J. Tucker, Ph.D.*
Graham Wright, B.Sc.
Wendy D. W. Brockman, B.A.
Hilton I. Kort, M.D.

FERTILITY AND STERILITY®
Vol. 68, No. 3, September 1997

Objective: To analyze the efficacy of intracytoplasmic sperm injection (ICSI) for "rescue" of failed conventional insemination cycles.
Design: Retrospective clinical study.
Setting: Private infertility clinic.
Patient(s): Fifty-four couples with non–male factor infertility undergoing routine IVF within our clinic.
Intervention(s): Twenty- to 24-hour-old unfertilized mature oocytes from conventional IVF cycles in which fertilization failure was complete were reinseminated by ICSI to attempt late fertilization and rescue of the otherwise failed IVF cycle.
Main Outcome Measure(s): Late fertilization, pregnancy, and embryonic implantation.
Result(s): Intracytoplasmic sperm injection reinsemination of 489 unfertilized mature oocytes caused degeneration in 50 (10.2%) oocytes, gave rise to normal fertilization in 215 (44.0%) of the injected oocytes, and allowed ET in 48 of the 54 cycles in which initial complete fertilization failure had occurred. One hundred sixty-four (76.3%) of 215 late-fertilized oocytes either were used for fresh transfer or were frozen-stored. Eight viable pregnancies resulted, yielding a 14.8% pregnancy rate per initiated cycle.
Conclusion(s): Barring potential concerns regarding the chromosomal normality of embryos arising from reinsemination, our results suggest that ICSI is a relatively successful means of rescuing conventional IVF cycles in which fertilization fails completely. (Fertil Steril® 1997;68:488–91. © 1997 by American Society for Reproductive Medicine.)

Fertilization failure

Embryo developmental potential of microsurgically corrected human three-pronuclear zygotes

Hai-xia Jin, Shan-jun Dai, Wen-yan Song, Gui-dong Yao, Sen-lin Shi & Ying-pu Sun

Syst Biol Reprod Med, 2015; 61(2): 96–102

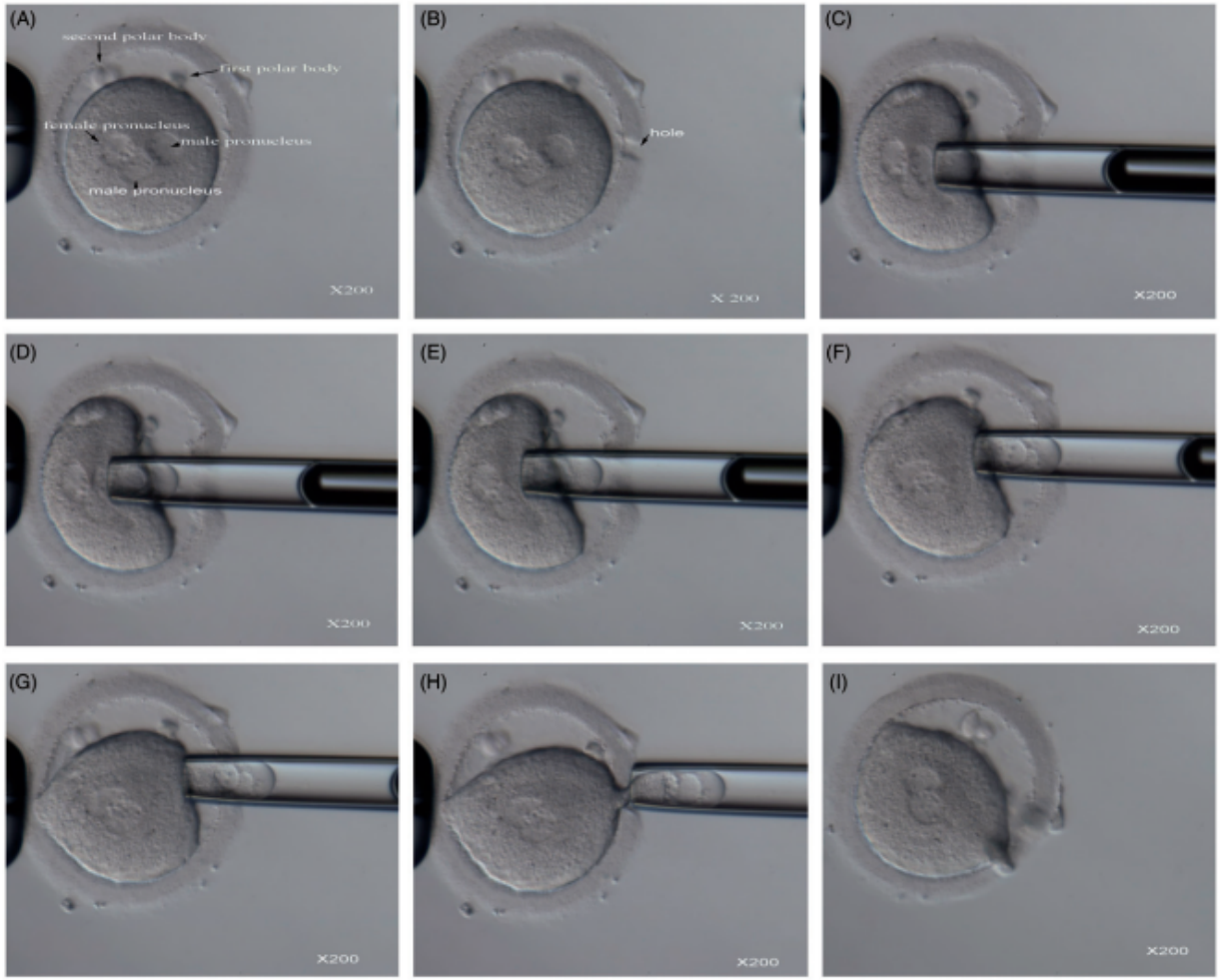


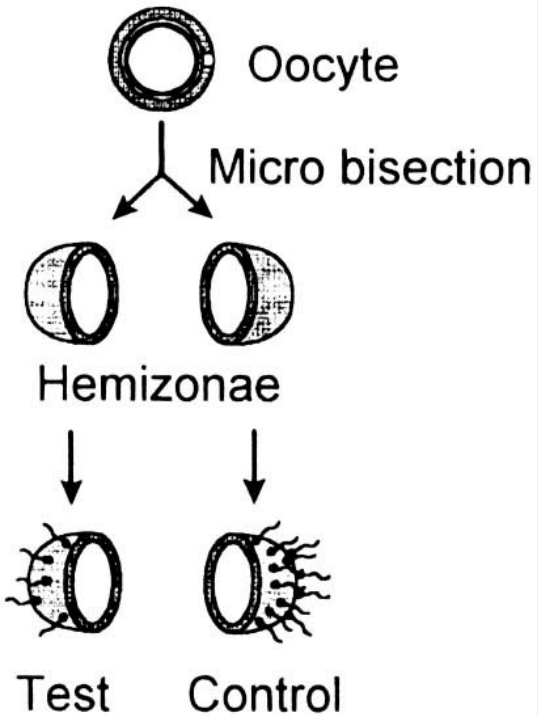
Table 3. Embryo development potential in 3 → 2PN, 3PN, and 2PN groups.

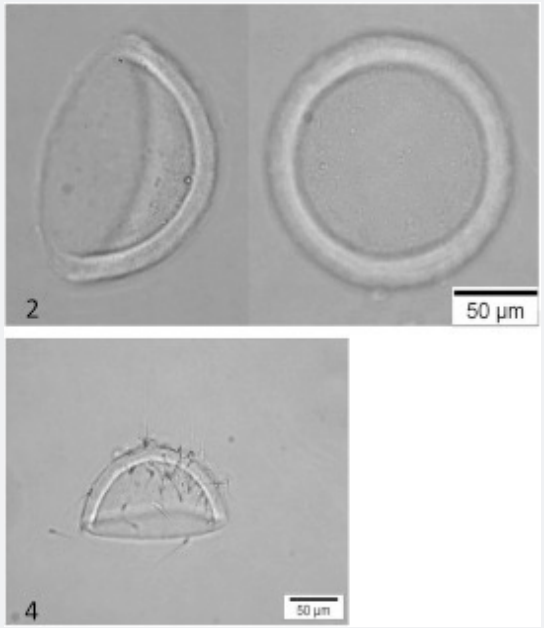
Items	3 → 2PN group	3PN group	2PN group
Zygotes (*n*)	314	381	359
Cleavage rate(%)	96.5 (302/314)	99.1 (378/318)	98.6 (354/359)
D3 6–8 cell embryo rate(%)	91.1 (275/302)	95.0 (359/378)	85.6 (303/354)†
D3 high-quality embryo rate%	88.1 (266/302)	87.6 (331/378)	65.5 (232/354)#†
Total blastulation rate(%)	21.5 (65/302)	5.6 (21/378)#	58.8% (208/354)#†
High-quality blastulation rate(%)	17.2 (52/302)	4.8 (18/378)#	50.1 (180/354)#†
D5 blastulation rate(%)	8.9 (27/302)	1.9 (7/378)#	53.7 (190/354)#†
D6 blastulation rate(%)	12.6 (38/302)	3.7 (14/378)#	5.1 (18/354)#

3 → 2PN: human three-pronuclear zygotes (3PN) corrected to two-pronuclear zygotes (2PN); D: day; †indicates $P<0.01$, compare to 3PN group; # indicates $P<0.01$, compare to 3 → 2PN group

The hemizona assay (HZA): Development of a diagnostic test for the binding of human spermatozoa to the human hemizona pellucida to predict fertilization potential

Burkman LJ; Coddington CC; Franken DR; et al
The Jones Institute for Reproductive Medicine, Department of Obstetrics and Gynecology, Eastern Virginia Medical School, Norfolk VA 23507, USA
FERTIL. STERIL.; 49/4 (688—697)/1988/



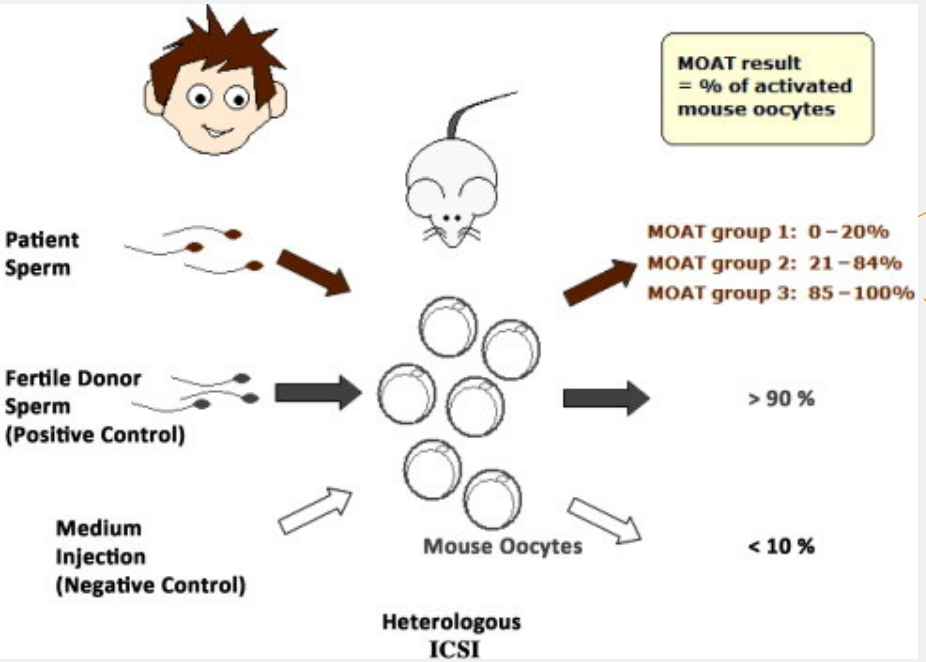


HZA index = $\frac{\text{bound sperm from subfertile male}}{\text{bound sperm from fertile male}}$ X 100

Treatment option for sperm- or oocyte-related fertilization failure: assisted oocyte activation following diagnostic heterologous ICSI

B.Heindryckx[1], J.Van der Elst, P.De Sutter and M.Dhont

Human Reproduction Vol.20, No.8 pp. 2237–2241, 2005



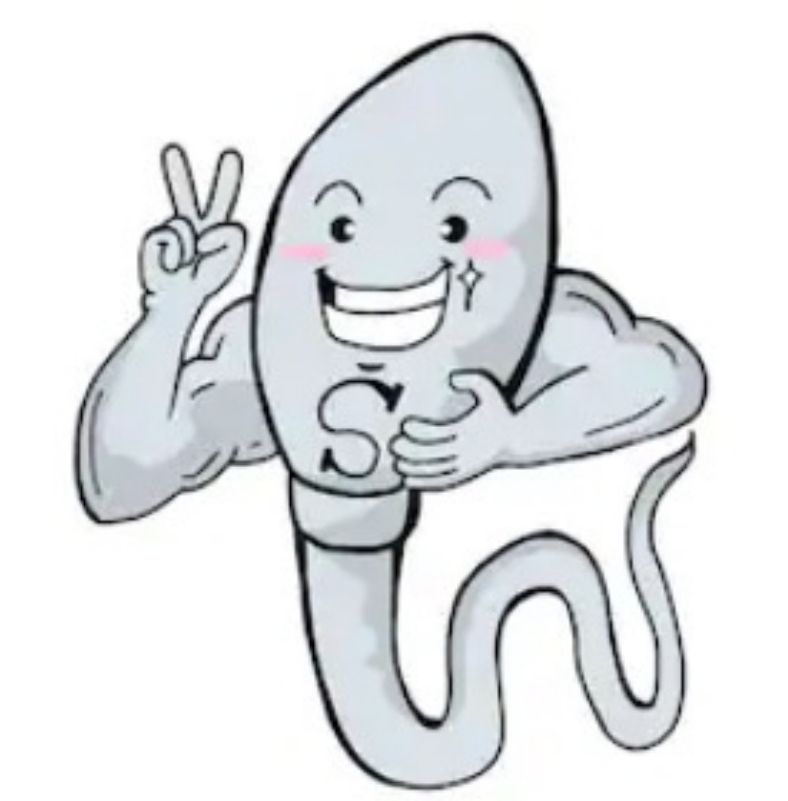
Sperm problem

Oocyte problem

VRIJE UNIVERSITEIT BRUSSEL

Universitair Ziekenhuis Brussel

What if no male factor is involved?



- **IVM**
- **Advanced Maternal Age**
- **Poor/low response**

- **Oocyte vitrification**

- **Genetic testing**
- Frozen sperm
- Serodiscordance

IVM

IVF versus ICSI for the fertilization of in-vitro matured human oocytes

Reproductive BioMedicine Online (2012) 25, 603–607

M Walls [a,b,*], S Junk [a], JP Ryan [a], R Hart [a,b]

Table 1 Recruited patient outcomes of IVM treatment.

	IVM–IVF	*IVM–ICSI*
Oocytes		
Total	72	78
Per patient	9.0 ± 2.83	9.75 ± 2.55
Oocytes matured		
Total	57/72 (79.2)	56/78 (71.8)
Per patient	7.1 ± 2.23	7.0 ± 1.6
Matured oocytes fertilized		
Total	34/57 (59.6)	38/56 (67.9)
Per patient	4.2 ± 2.05	4.75 ± 1.16
Useable blastocysts formed		
Total	14/34 (41.2)	18/38 (47.4)
Per patient	1.75 ± 1.39	2.25 ± 1.04
Blastocysts formed		
Total	21/34 (61.8)	21/38 (55.3)
Per patient	2.6 ± 1.5	2.63 ± 1.06

Values are *n*, *n*/total (%) or mean ± SD.
There were no statistically significant differences between the two groups.
ICSI = intracytoplasmic sperm injection; IVM = in-vitro maturation.

Table 2 Comparison of embryonic outcomes according to fertilization technique.

	IVF	*ICSI*
Useable blastocysts	14	18
Vitrified blastocysts	12	13
Embryos transferred	7	7
Fresh cycle	2	5
Cryopreserved cycle	5	2
Sacs/fetal heart	3	3
Cumulative implantation rate (%)	42.86	42.86

Values are *n* unless otherwise stated.
ICSI = intracytoplasmic sperm injection.

IVM

The effect of insemination methods on *in vitro* maturation outcomes

Clin Exp Reprod Med 2020;47(2):130-134

Pallop Pongsuthirak

Variable	IVM/IVF	IVM/ICSI	*p*-value[a]
Immature oocyte	416	412	-
Mature oocyte[b]	325 (78.1)	299 (72.6)	0.076
Normal fertilization	193 (59.4)	200 (66.9)	0.063
Blastocyst	117 (60.6)	107 (53.5)	0.186
High-quality blastocyst	79 (40.9)	93 (46.5)	0.314

Variable	IVM/IVF	IVM/ICSI	*p*-value[a]
High-quality blastocyst	76	93	NS
Vitrified blastocyst	55	72	NS
Embryos transferred	21	21	-
Fresh cycle	18	19	NS
Cryopreserved cycle	3	2	NS[b]
Implantation	11 (52.2)	10 (47.6)	NS
Clinical pregnancy	9 (42.9)	9 (42.9)	NS

AMA-low oocyte yield

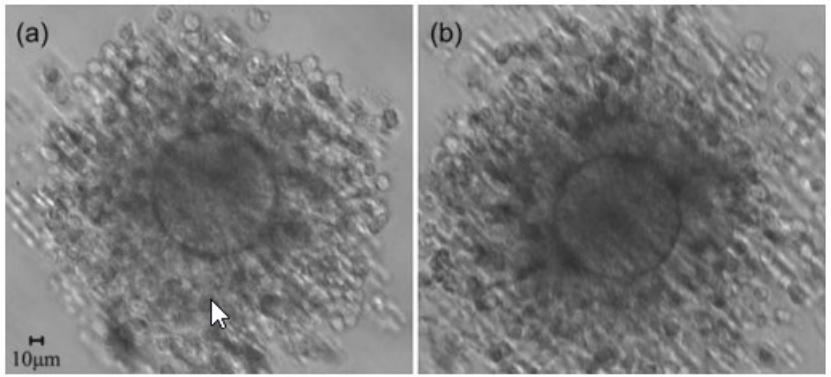
		TopQ E	CPR IVF-ICSI	LBR IVF-ICSI	Age
Tannus et al., 2017	AMA		19.1%-15.6% (0.24)	9.9%-9.2% (0.14)	41.1
Liu et al., 2018	AMA	38.79%-41.55% (0.32)	21.59%-13.25% (0.08)	12.16%-6.02% (0.11)	41.3
Haas et al., 2021	AMA	41.2%-41% (0.8)			41.1
Gennarelli et al., 2019	Unexplained infertility		10.4%-10.6% (0.7567)	6.3%-6.6% (0.9315)	41.1
Kim et al., 2014	Low oocyte yield (1.8)	72.2%-69.9% (NS)	35%-19.1% (NS)		33.4-37.3
Ou et al., 2010	Low oocyte yield (2.5)		21.6%-38.5% (0.175)	13.7%-30.8% (0.126)	36.0
Guo et al., 2018	Low oocyte yield (1.0)		12.3%-11.8% (0.914)	7.8%-7.3% (0.896)	36.1

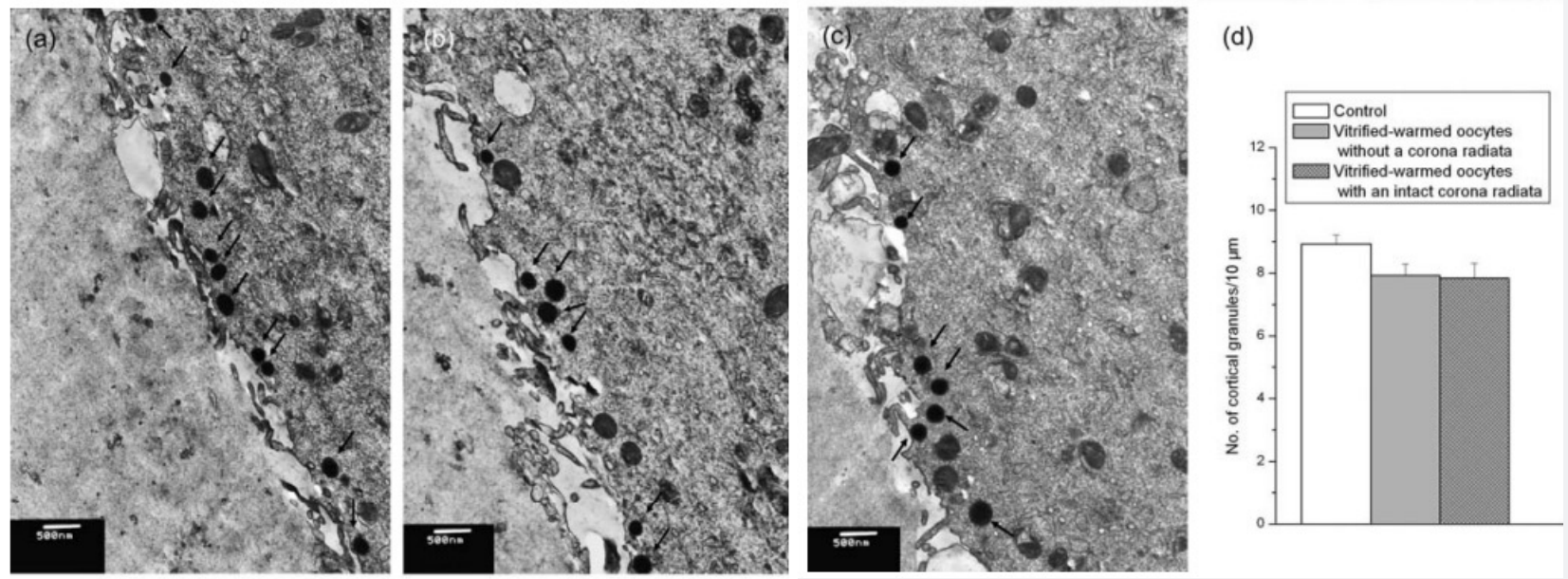
Oocyte vitrification

Fertilization rates are improved after IVF if the corona radiata is left intact in vitrified-warmed human oocytes

Xian-Hong Tong [1,2,†], Li-Min Wu [1,†], Ren-Tao Jin [1], Li-Hua Luo [1], Hong-Bing Luan [1], and Yu-Sheng Liu [1,*]

Human Reproduction, Vol.27, No.11 pp. 3208–3214, 2012





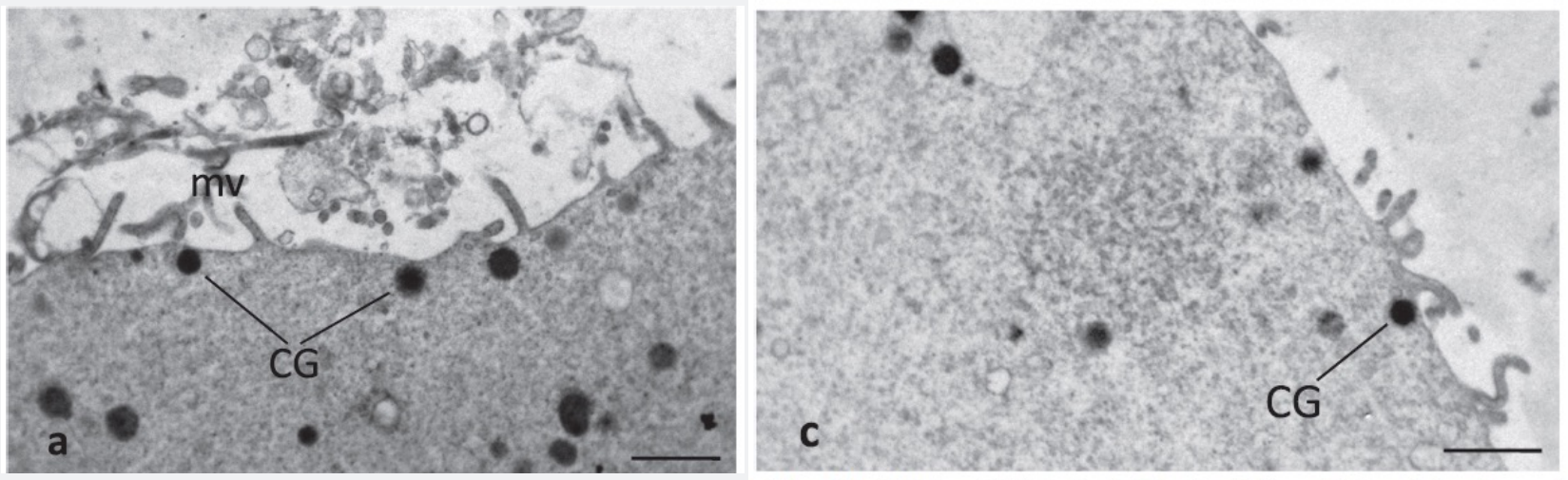
Oocyte vitrification

Table II Survival, fertilization and developmental competence of the vitrified-warmed oocytes after conventional IVF.

Parameter	Group			
	Vitrified-warmed oocytes without a corona radiata ($n = 49$)	Vitrified-warmed oocytes with a corona radiata ($n = 49$)	Fresh oocytes without a corona radiata ($n = 53$)	Fresh oocytes with a corona radiata ($n = 54$)
Survival rate (%)	98.0 (48/49)	98.0 (48/49)	—	—
Fertilization rate (2PN, %)	18.8 (9/48)▲▲▲	77.1 (37/48)***	22.6 (12/53)▲▲▲	74.1 (40/54)
Abnormal fertilization rate (%)	0	2.1 (1/49)	0	1.9 (1/54)
Cleavage rate (%)	100 (9/9)	100 (37/37)	100 (12/12)	100 (40/40)
Top embryo quality rate (%)	66.7 (6/9)	64.9 (24/37)	66.7 (8/12)	65.0 (26/40)
Mean #number of embryos for ET (N ± SD)	—	2.0 ± 0	—	2.0 ± 0
Singletons	—	3	—	2
Triplets	—	0	—	0
Twins	—	1	—	2
Implantation rate (%)	—	31.3 (5/16)	—	37.5 (6/16)
Spontaneous abortions (n)	—	1	—	1
Baby take home rate (%)	—	37.5 (3/8)	—	37.5 (3/8)

***$P < 0.001$ versus vitrified-warmed oocytes without a corona radiata, ▲▲▲$P < 0.001$ versus fresh oocytes with an intact corona radiata.

Oocyte vitrification



Cortical granules: Nottola et al., 2009, Gualtieri et al., 2011; Bianchi et al., 2014; Palmerini et al., 2014

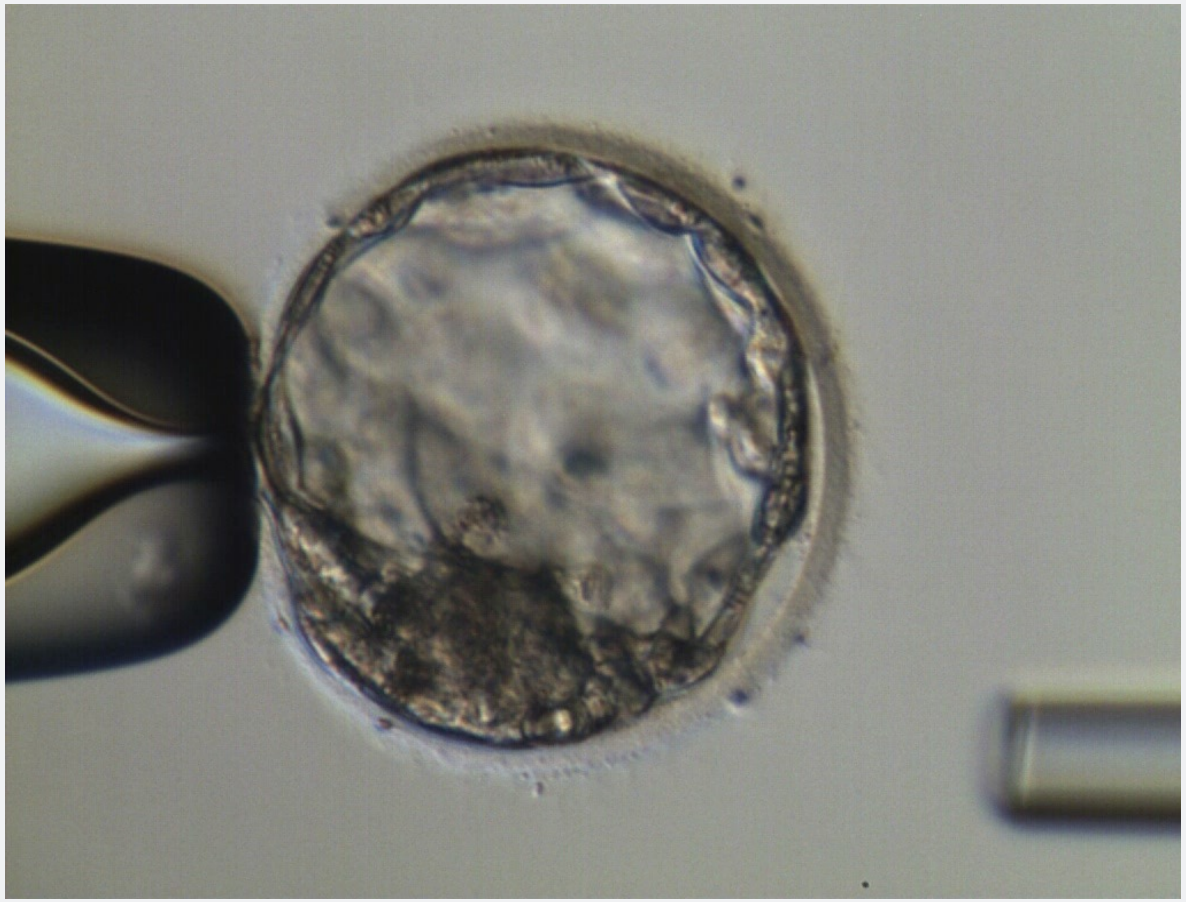
PGT-A

ICSI

- ensure monospermic fertilization
- eliminate potential paternal contamination from extraneous sperm attached to the zona pellucida
- prevent the presence of non-decondensed sperm within blastomeres or cumulus cells

Thornhill et al., 2006; ESHRE Capri Workshop group, 2007, PGDIS meeting 2019, Harton et al., 2011; ASRM, 2012; Berger and Baker, 2014

IVF versus ICSI: PGT-A



Human Reproduction, Vol.35, No.2, pp. 317–327, 2020
Advance Access Publication on February 22, 2020 doi:10.1093/humrep/deaa002

human reproduction | ORIGINAL ARTICLE *Embryology*

Intracytoplasmic sperm injection is not superior to conventional IVF in couples with non-male factor infertility and preimplantation genetic testing for aneuploidies (PGT-A)

Neelke De Munck[1,*], Ibrahim El Khatib[1], Andrea Abdala[1], Ahmed El-Damen[1], Aşina Bayram[1], Ana Arnanz[1], Laura Melado[1], Barbara Lawrenz[1,2], and Human M. Fatemi[1]

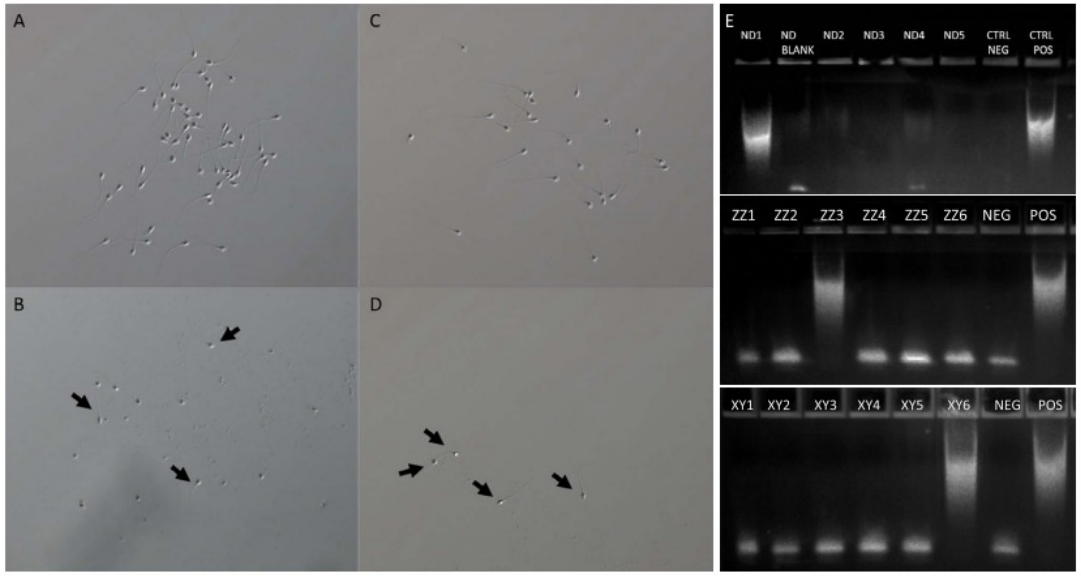


Figure 1 **Validation whole genome amplification of sperm. A:** sperm cells ($n = 60$) selected for tubing; **B:** sperm cells left in the drop ($n = 3$; arrow) after visual selection of the sperm under the microscope; **C:** sperm cells ($n = 24$) selected for tubing; **D:** sperm cells left in the drop ($n = 4$; arrow) after visual selection of the sperm under the microscope. **E:** WGA results from the three experiments (ND = Experiment 1, ZZ = Experiment 2, XY = Experiment 3); ND1: positive control, ND Blank: negative control, ND2: 60 sperm, ND3: 25 sperm, ND4: 60 sperm, ND5: 25 sperm; ZZ1: 20 sperm, ZZ2: 20 sperm, ZZ3; positive control, ZZ4; negative control, ZZ5: 3 sperm, ZZ6: 10 sperm; XY1: 10 sperm, XY2: 10 sperm, XY3: 3 sperm, XY4: 2 sperm, XY5: negative control, XY6: positive control.

IVF versus ICSI: PGT-A

Table III **Blastocyst biopsy and euploid blastocysts.**

	IVF	ICSI	*P value*	OR [95% CI]
Blastocyst biopsy				
Day 5 (average ± SD)	2.7 ± 2.7	2.6 ± 2.1	0.941	
Day 5 (%)	60.1 ± 27.6	55.7 ± 35.5	0.244	0.77769 [0.51768–1.16827]
Day 6 (average ± SD)	1.3 ± 0.8	1.2 ± 1.2	0.758	
Day 6 (%)	37.4 ± 26.9	34.3 ± 32.2	0.846	1.08812 [0.46696–2.53556]
Day 7 (average ± SD)	0.07 ± 0.3	0.03 ± 0.2	NA	
Day 7 (%)	2.5 ± 10.1	3.3 ± 18.3	NA	NA
Total (average ± SD)	4.0 ± 2.8	3.9 ± 2.5	0.774	
Total (%)	67.4 ± 22.1	60.6 ± 29.6	0.619	1.10702 [0.74608–1.64256]
Euploid blastocysts				
Day 5 (average ± SD)	1.4 ± 1.7	1.5 ± 1.4	0.923	
Day 5 (%)	65.9 ± 41.1	64.2 ± 42.2	0.2213	0.67798 [0.41340–1.11190]
Day 6 (average ± SD)	0.53 ± 0.7	0.4 ± 0.6	0.425	
Day 6 (%)	24.0 ± 35.4	15.8 ± 27.9	0.484	1.52163 [0.47714–4.85261]
Day 7 (average ± SD)	0.0 ± 0.0	0.0 ± 0.0	NA	
Day 7 (%)	0 (0.0)	0 (0.0)	NA	NA
Total (average ± SD)	2.0 ± 1.8	1.9 ± 1.7	0.808	
Total (%)	49.8 ± 28.8	44.1 ± 34.6	0.755	1.05664 [0.75188–1.48494]

Total number of blastocysts biopsied and euploid per day of biopsy (5, 6 or 7). Blastocyst biopsy expressed per normally fertilised oocytes; euploid blastocysts expressed per blastocyst biopsied. Results are expressed as average ± SD per cycle ($n = 30$) or % ± SD per cycle ($n = 30$). SD: standard deviation, NA: not applicable. Degrees of freedom: 1.

REVIEWS

NATURE REVIEWS | UROLOGY

Intracytoplasmic sperm injection for male infertility and consequences for offspring

Sandro C. Esteves[1,2,3], Matheus Roque[4], Giuliano Bedoschi[5], Thor Haahr[3,6] and Peter Humaidan[3,6]*

Table 1 | **Fertilization methods in male factor and non-male factor infertility**

Type of infertility	Fertilization method	Refs
Male factor infertility		
Azoospermia	ICSI mandatory	15–20
Severe OAT	ICSI highly recommended	25
Moderate OAT	IVF and ICSI equally effective	26
Isolated teratozoospermia	IVF and ICSI equally effective	32–36
Absolute asthenozoospermia	ICSI mandatory	19,37,38
Globozoospermia	ICSI mandatory	39,40
Antisperm antibodies	IVF and ICSI equally effective	42
Sperm DNA fragmentation	ICSI recommended	49–56,175
Non-male factor infertility		
General non-male factor population	Equally effective, slightly in favour of IVF	4,6,12,57,60
Unexplained infertility	Equally effective, but sibling oocyte studies suggest that ICSI is superior to IVF for fertilization, whereas the reproductive outcome is not significantly different	6,57–60
Poor-quality oocytes and advanced maternal age	Equally effective, slightly in favour of IVF	61,62,65
Poor responders	Equally effective, slightly in favour of IVF	62,65
Preimplantational genetic testing	ICSI highly recommended	13,22,68,69
Tubal ligation	IVF preferable	76
Serodiscordant couples	Equally effective	77,78

ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; OAT, oligoasthenoteratozoospermia.

Journal of Assisted Reproduction and Genetics (2021) 38:101–123
https://doi.org/10.1007/s10815-020-01987-0

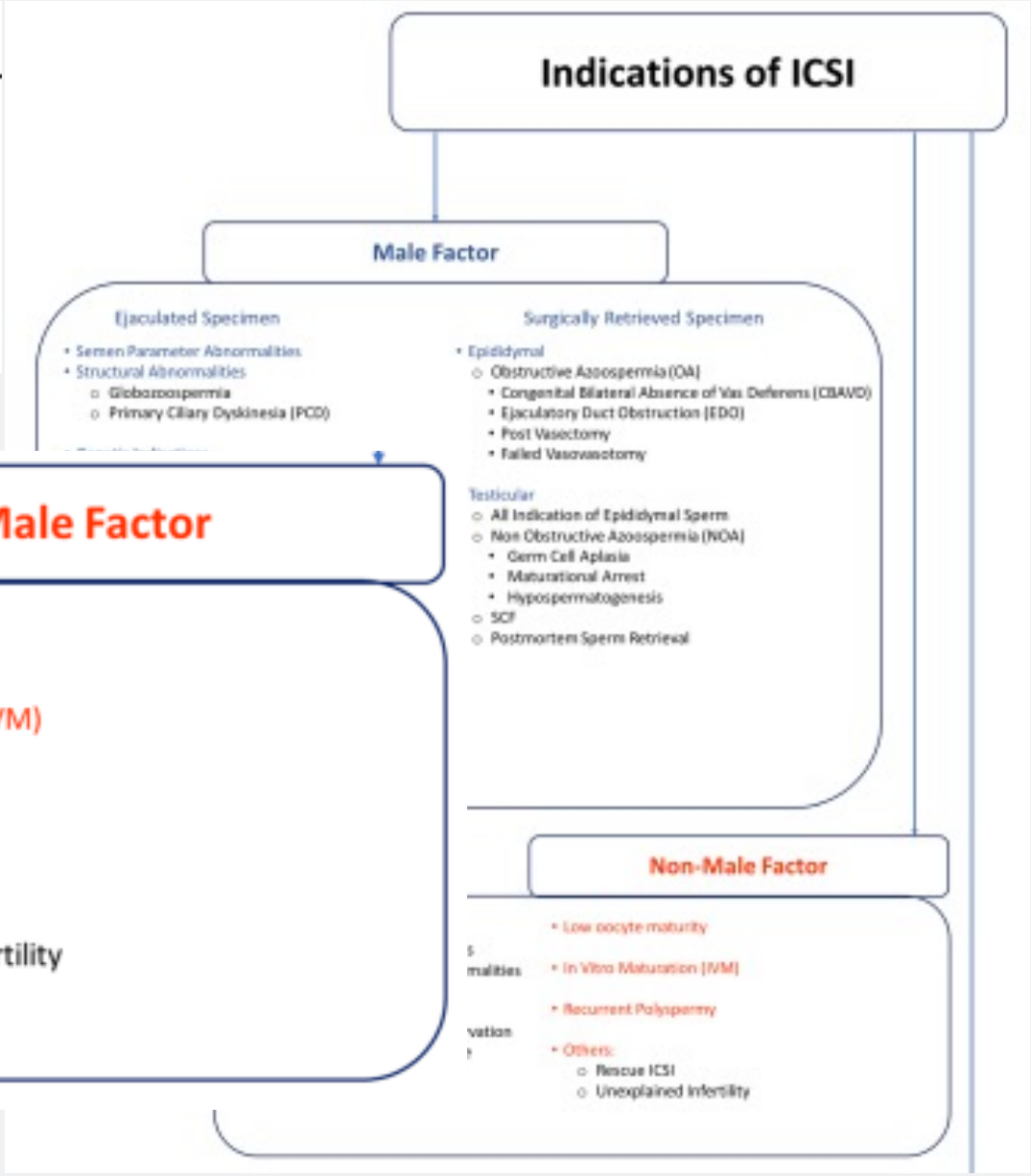
REVIEW

Thoughts on the popularity of ICSI

Mounia Haddad[1] · Joshua Stewart[1] · Philip Xie[1] · Stephanie Cheung[1] · Aysha Trout[1] · Derek Keating[1] · Alessandra Parrella[1] · Sherina Lawrence[1] · Zev Rosenwaks[1] · Gianpiero D. Palermo[1]

Non-Male Factor

- Oocyte Dysmorphism
  - Zona Pellucida Abnormalities
  - Oolemma/Ooplasmic Abnormalities
- Fertility Preservation
  - Elective Oocyte Cryopreservation
  - Medically-indicated Oocyte Cryopresevation
- Low oocyte maturity
- In Vitro Maturation (IVM)
- Recurrent Polyspermy
- Others:
  - Rescue ICSI
  - Unexplained Infertility



Gartner hype cycle - ICSI

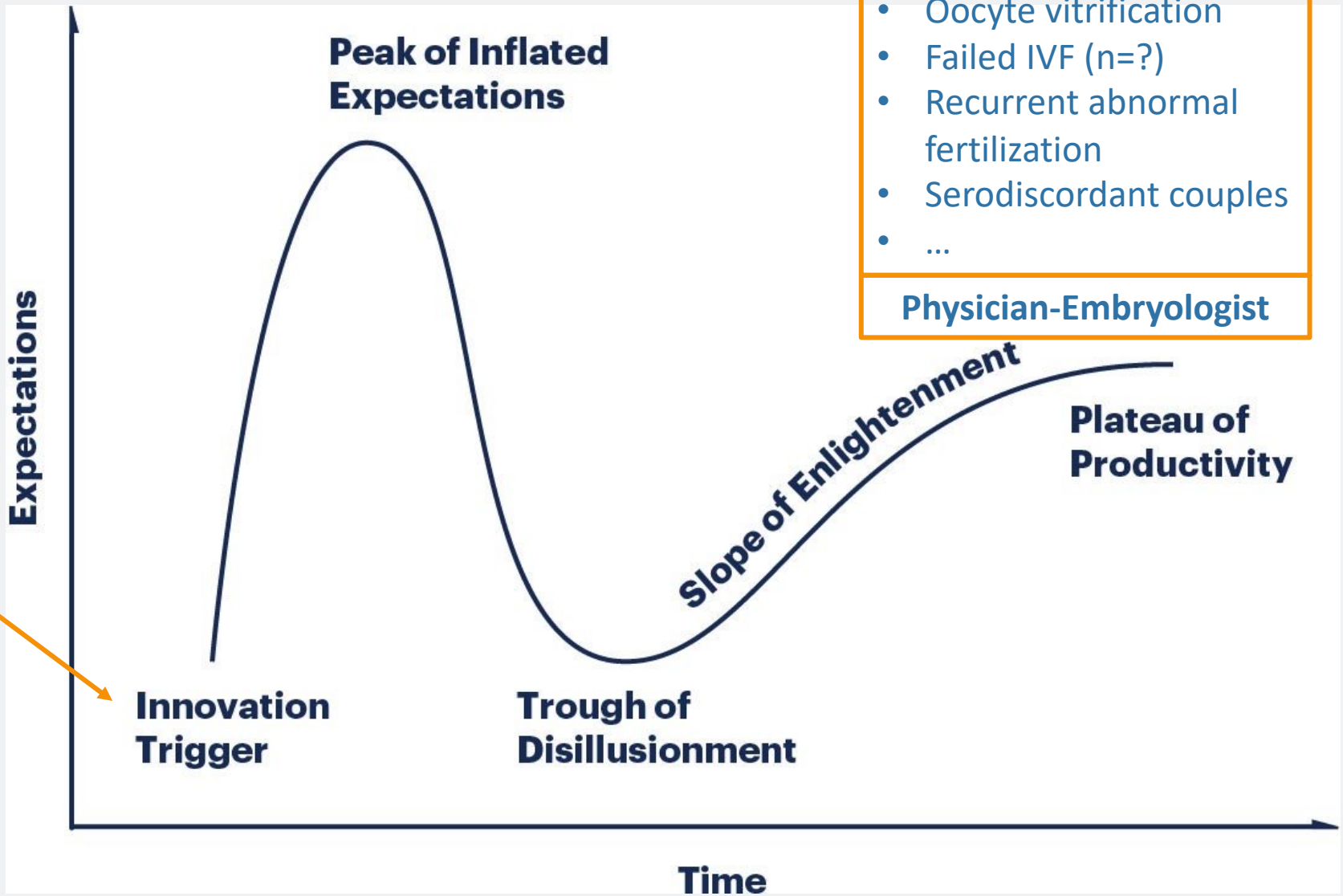
- PGT-M/SR
- IVM
- Oocyte vitrification
- Failed IVF (n=?)
- Recurrent abnormal fertilization
- Serodiscordant couples
- …

Physician-Embryologist

Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte

GIANPIERO PALERMO HUBERT JORIS
PAUL DEVROEY ANDRE C. VAN STEIRTEGHEM

VOL 340: JULY 4, 1992 THE LANCET



Thank you!

Brussels IVF

Neelke.DeMunck@uzbrussel.be

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Universitair Ziekenhuis Brussel